AUSTRALIAN PRODUCT INFORMATION

ZOELY®

(nomegestrol acetate and estradiol (as hemihydrate)) Tablets

1 NAME OF THE MEDICINE

Nomegestrol acetate and estradiol (as hemihydrate)

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each blister strip consists of 24 white active tablets each containing 2.5 mg nomegestrol acetate and 1.5 mg estradiol (as hemihydrate) and 4 yellow placebo tablets that do not contain active substances.

List of excipients with known effect:

- Lactose

For the full list of excipients, see Section 6.1 List of excipients.

3 PHARMACEUTICAL FORM

Each blister of ZOELY contains:

- 24 white, round, active film-coated tablets coded with ‘ne’ on both sides, each containing 2.5 mg nomegestrol acetate and 1.5 mg estradiol.
- 4 yellow, round, placebo film-coated tablets coded with ‘p’ on both sides.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Oral contraception.

4.2 DOSE AND METHOD OF ADMINISTRATION

How to take ZOELY

Tablet intake instructions are the same for all users.

Tablets must be taken every day at about the same time without regard to meals. Take tablets with some liquid as needed, and in the order as directed on the package. One tablet is to be taken daily for 28 consecutive days. Each pill pack starts with 24 white active tablets, followed by 4 yellow placebo tablets; (see Figure 1). A subsequent pack is started immediately after finishing the previous pack, without a break in daily tablet intake and irrespective of presence or absence of withdrawal bleeding. Withdrawal bleeding usually starts on day 2-3 after intake of the last white tablet and may not have finished before the next pack is started. See also Section 4.4 Special warnings and precautions for use, Cycle control.

How to start ZOELY

No preceding hormonal contraceptive use
Tablet-taking has to start on day 1 of the woman's natural cycle (i.e. the first day of her menstrual bleeding). When doing so, no additional contraceptive measures are necessary. Starting on days 2-5 is allowed, but during the first pill pack a barrier method should be used until the woman has completed 7 days of uninterrupted white tablet-taking (see Figure 1).

Changing from a combined hormonal contraceptive (combined oral contraceptive (COC), vaginal ring or transdermal patch)
The woman should start with ZOELY preferably on the day after the last active tablet (the last tablet containing the active substances) of her previous COC, but at the latest on the day following the usual tablet-free or placebo tablet interval of her previous COC. In case a vaginal ring or transdermal patch has been used, the woman should start using ZOELY preferably on the day of removal, but at the latest when the next application would have been due.

If the woman has been using her previous method consistently and correctly, and if it is reasonably certain that she is not pregnant, she may also switch on any day. The hormone-free interval of the previous method should never be extended beyond its recommended length.

Changing from a progestagen-only-method (minipill, implant, injectable) or from a hormone-medicated Intra Uterine System (IUS)
The woman may switch any day from the minipill and ZOELY should be started on the next day. An implant or IUS may be removed any day, and ZOELY should be started on the day of its removal. When changing from an injectable, ZOELY should be started on the day when the next injection would have been due. In all of these cases the woman should be advised to additionally use a barrier method until she has completed 7 days of uninterrupted white active tablet-taking.

Following first-trimester abortion
The woman may start immediately. When doing so, no additional contraceptive measures are necessary.

Following delivery or second-trimester abortion
For breast-feeding women see Section 4.6 Fertility, pregnancy and lactation**,** Use in lactation.

Women should be advised to start between day 21 and 28 after delivery or second-trimester abortion. When starting later, the woman should be advised to additionally use a barrier method for the first 7 days of white active tablet taking. However, if intercourse has already occurred, pregnancy should be excluded before the actual start of COC use or the woman has to wait for her first menstrual period. The increased risk of thromboembolism in the puerperium must be considered if recommencing ZOELY (see Section 4.4 Special warnings and precautions for use).

Management of missed tablets

The following advice only refers to missed white active tablets:

If the woman is **less than 24 hours** late in taking any active tablet, contraceptive protection is not reduced. The woman should take the tablet as soon as she remembers and should take further tablets at the usual time.

If the woman is **24 or more hours** late in taking any active tablet, contraceptive protection may be reduced. The management of missed tablets can be guided by the following two basic rules:

- 7 days of uninterrupted 'white active tablet'-taking are required to attain adequate suppression of the hypothalamic-pituitary-ovarian-axis.
- The more 'white active tablets' are missed and the closer the missed tablets are to the 4 yellow placebo tablets, the higher the risk of a pregnancy.

Figure 1

Day 1-7 of active tablet intake

The woman should take the last missed white tablet as soon as she remembers even if this means taking two tablets at the same time. She then continues to take tablets at her usual time. In addition, a barrier method such as a condom should be used until she has completed 7 days of uninterrupted white tablet-taking. If intercourse took place in the preceding 7 days, the possibility of a pregnancy should be considered.

Day 8-17 of active tablet intake

The woman should take the last missed white tablet as soon as she remembers, even if this means taking two tablets at the same time. She then continues to take tablets at her usual time. Provided that the woman has taken her tablets correctly in the 7 days preceding the first missed tablet, there is no need to use extra contraceptive precautions. However, if she has missed more than 1 tablet, the woman should be advised to use extra precautions until she has completed 7 days of uninterrupted white tablet-taking.

Day 18-24 of active tablet intake

The risk of reduced reliability is imminent because of the forthcoming yellow placebo-tablet phase. However, by adjusting the tablet-intake schedule, reduced contraceptive protection can still be prevented. By adhering to either of the following two options, there is therefore no need to use extra contraceptive precautions, provided that in the 7 days preceding the first missed tablet the woman has taken all tablets correctly. If this is not the case, she should follow the first of these two options and use extra precautions for the next 7 days as well.

1. The woman should take the last missed tablet as soon as she remembers, even if this means taking two tablets at the same time. She then continues to take tablets at her usual time until the active tablets are used up. The 4 placebo tablets from the last row must be discarded. The next blister pack must be started right away. The woman is unlikely to have a withdrawal bleed until the end of the active tablets section of the second pack, but she may experience spotting or breakthrough bleeding on tablet-taking days.
2. The woman may also be advised to discontinue active tablet-taking from the current blister pack. She should then take placebo tablets from the last row for a maximum of 3 days such that the total number of placebo plus missed active white tablets is not more than 4, and subsequently continue with the next blister pack.

If the woman missed tablets and subsequently has no withdrawal bleed in the placebo tablet phase, the possibility of a pregnancy should be considered.

Please note: If the woman is not sure about the number or colour of tablets missed and what advice to follow, a barrier method should be used until she has completed 7 days of uninterrupted white active tablet-taking.

Yellow placebo tablets missed

Contraceptive protection is not reduced. Yellow tablets from the last (4th) row of the blister can be disregarded. However, the missed tablets should be discarded to avoid unintentionally prolonging the placebo tablet phase.

Advice in case of gastro-intestinal disturbances

In case of severe gastro-intestinal disturbance (e.g., vomiting or diarrhoea), absorption of the active substances may not be complete and additional contraceptive measures should be taken. If vomiting occurs within 3-4 hours after white tablet-taking, the tablet should be considered as missed and a new tablet should be taken as soon as possible. The new tablet should be taken within 24 hours of the usual time of tablet-taking if possible. The next tablet should then be taken at the usual time. If more than 24 hours have passed since last pill intake, the advice concerning missed tablets as given in ‘Management of missed tablets’, is applicable. If the woman does not want to change her normal tablet-taking schedule, she has to take the extra white tablet(s) from another pack.

How to shift periods or how to delay a period

To delay a period the woman should continue with another blister pack of ZOELY without taking the yellow placebo tablets from her current pack. The extension can be carried on for as long as wished until the end of the white active tablets in the second pack. Regular intake

of ZOELY is then resumed after the yellow placebo tablets have been taken of the second pack. During the extension the woman may experience breakthrough bleeding or spotting.

To shift her periods to another day of the week than the woman is used to with her current scheme, she can be advised to shorten her forthcoming yellow placebo tablet phase with a maximum of 4 days. The shorter the interval, the higher the risk that she does not have a withdrawal bleed and may experience breakthrough-bleeding and spotting during the subsequent pack (just as when delaying a period).

4.3 CONTRAINDICATIONS

Combined hormonal contraceptives (CHCs) should not be used in the presence of any of the conditions listed below. ZOELY should be stopped immediately should any of the following conditions appear for the first time during the use of ZOELY:

- Presence or risk of venous thromboembolism (VTE) (see Section 4.4 Special warnings and precautions for use)
    - Current VTE (on anticoagulants) or history of deep venous thrombosis [DVT] or pulmonary embolism [PE].
    - Known hereditary or acquired predisposition for venous thromboembolism, such as APC-resistance (including Factor V Leiden), antithrombin-III-deficiency, protein C deficiency, protein S deficiency hyperhomocysteinaemia, antiphospholipid-antibodies (eg. anticardiolipin-antibodies and lupus anticoagulant).
    - Major surgery with prolonged immobilisation.
    - A high risk of venous thromboembolism due to the presence of multiple risk factors.
- Presence or risk of arterial thromboembolism (ATE) (see Section 4.4 Special warnings and precautions for use)
    - Current ATE or history of ATE (e.g. myocardial infarction or stroke) or prodromal condition (e.g. angina pectoris or transient ischaemic attack [TIA]).
    - Known hereditary or acquired predisposition for arterial thromboembolism, such as hyperhomocysteinaemia and antiphospholipid-antibodies (eg. anticardiolipin-antibodies and lupus anticoagulant), APC-resistance (including Factor V Leiden), antithrombin-III-deficiency, protein C deficiency, protein S deficiency.
- History of migraine with focal neurological symptoms;
- A high risk of arterial thromboembolism due to multiple risk factor(s) or the presence of one serious risk factor such as:
    - diabetes mellitus with vascular symptoms
    - severe hypertension
    - severe dyslipoproteinemia
- Pancreatitis or a history thereof if associated with severe hypertriglyceridaemia;
- Presence or history of severe hepatic disease as long as liver function values have not returned to normal;
- Presence or history of liver tumours (benign or malignant);
- Known or suspected sex steroid-influenced malignancies (e.g., of the genital organs or the breasts);
- Meningioma or history of meningioma;
- Known or suspected pregnancy;

- Hypersensitivity to any of the active substances of ZOELY or to any of the excipients.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

If any of the conditions/risk factors mentioned below is present, the benefits of the use of ZOELY should be weighed against the possible risks for each individual woman and discussed with the woman before she decides to start using ZOELY. In the event of aggravation, exacerbation or first appearance of any of these conditions or risk factors, the woman should contact her physician. The physician should then decide on whether its use should be discontinued. All data presented below are based upon epidemiological data obtained with combined oral contraceptives (COCs) containing ethinylestradiol. ZOELY contains 17β-estradiol. The warnings are considered applicable to the use of ZOELY.

Circulatory disorders

Risk of venous thromboembolism (VTE)

Epidemiological studies have shown an association between the use of combined oral contraceptives (COCs) containing ethinylestradiol and an increased risk of venous thrombotic and thromboembolic diseases such as deep venous thrombosis and pulmonary embolism. These events occur rarely in average risk women.

Use of any ethinylestradiol-containing COC carries an increased risk of venous thromboembolism (VTE) compared with no use. The excess risk of VTE is highest during the first year a woman ever uses a combined oral contraceptive. The risk is also increased after initially starting a COC or restarting the same or different COC after a break in use of 4 weeks or more. This increased risk is less than the risk of VTE associated with pregnancy, which is estimated as 5-20 cases per 10,000 woman-years for pregnant women. This compares with 1-5 cases per 10,000 woman-years for non-users. VTE is fatal in 1%-2% of cases. It is not known how ZOELY influences this risk compared with other COCs.

Extremely rarely, thrombosis has been reported to occur in other blood vessels, e.g. hepatic, mesenteric, renal, cerebral or retinal veins and arteries, in COC users. There is no consensus as to whether the occurrence of these events is associated with the use of COCs. The use of any CHC increases the risk of VTE compared with no use.

Products that contain the progestogens levonorgestrel, norgestimate or norethisterone are associated with the lowest risk of VTE. ZOELY may have a risk of VTE in the same range as observed with CHC containing levonorgestrel.

The decision to use any product other than one with the lowest VTE risk should be taken only after a discussion with the woman to ensure she understands the risk of VTE with CHCs, and how her current risk factors influence this risk.

Table 1: Risk[1] of developing a blood clot (VTE) in a year

Women not using a combined hormonal contraceptive (CHC) and not pregnant	About 1-5 out of 10,000 women[1]
Women using a CHC containing levonorgestrel, norethisterone or norgestimate	About 5-7 out of 10,000 women
Women using a CHC containing etonogestrel or norelgestromin	About 6-12 out of 10,000 women
Women using a CHC containing drospirenone, gestodene, desogestrel or cyproterone acetate[2]	About 9-12 out of 10,000 women
Women using a CHC containing chlormadinone acetate	Not yet known[3]
Women using a CHC containing dienogest and estradiol valerate	Not yet known[3]
Women using a CHC containing nomegestrol acetate and E2	May have a risk in the same range as observed with CHC containing levonorgestrel

[1] In any individual woman the risk may be far higher, depending on her underlying risk factors (see below).

[2] While cyproterone acetate is indicated for the treatment of moderate to severe acne related to androgen sensitivity and/or hirsutism, it is known to have efficacy as a contraceptive. The risk of VTE associated with cyproterone acetate use is considered to be 1.5 to 2 times higher than for CHCs containing levonorgestrel.

[3] Further studies are ongoing or planned to collect sufficient data to estimate the risk for these products. Where the risk for a particular progestogen is uncertain, the risk of the class should be used in determining the risk for the individual patient.

Note: Combined hormonal contraceptive (CHC) in the above table refers to oral contraceptives with a low estrogen dose (< 50 µg ethinylestradiol). An additional increase in VTE risk for CHCs containing ≥ 50 µg ethinylestradiol cannot be excluded.

The risk for venous thromboembolic complications in CHC users may increase substantially in a woman with additional risk factors, particularly if there are multiple risk factors (see Section 4.4 Special warnings and precautions for use, Risk factors for VTE).

ZOELY is contraindicated if a woman has multiple risk factors that put her at high risk of venous thrombosis. If a woman has more than one risk factor, it is possible that the increase in risk is greater than the sum of the individual factors – in this case her total risk of VTE should be considered. If the balance of benefits and risks is considered to be negative a CHC should not be prescribed.

The increased risk of thromboembolism in the puerperium must be considered if recommencing ZOELY (see Section 4.2 Dose and method of administration).

Women using COCs should be specifically pointed out to contact their physician in case of possible symptoms of thrombosis. In case of suspected or confirmed thrombosis, COC use should be discontinued. Adequate contraception should be initiated because of the teratogenicity of anti-coagulant therapy (coumarins).

Risk factors for VTE

- Obesity (body mass index over 30 kg/m²). Risk increases substantially as BMI rises.
- Prolonged immobilisation, major surgery, any surgery to the legs or pelvis, neurosurgery, or major trauma.
- Temporary immobilisation including air travel >4 hours can also be a risk factor for VTE, particularly in women with other risk factors.
- Positive family history (venous thromboembolism ever in a sibling or parent especially at a relatively early age e.g. before 50).
- Biochemical factors Activated Protein C (APC) resistance (including Factor V Leiden), antithrombin-III deficiency, protein C deficiency, protein S deficiency, hyperhomocysteinaemia, antiphospholipid antibodies (anticardiolipin antibodies, lupus anticoagulant).
- Other medical conditions associated with VTE
  - Cancer
  - Systemic lupus erythematosus
  - Haemolytic uraemic syndrome
  - Chronic inflammatory bowel disease (e.g. Crohn's disease or ulcerative colitis)
  - Sickle cell disease.
- Increasing age, particularly above 35 years.
- Smoking.

In women at risk of prolonged immobilisation (including major surgery, any surgery to the legs or pelvis, neurosurgery, or major trauma), it is advisable to discontinue use of ZOELY (in the case of elective surgery at least four weeks in advance) and not resume until two weeks after complete remobilisation. Another method of contraception should be used to avoid unintentional pregnancy. Antithrombotic treatment should be considered if ZOELY has not been discontinued in advance.

If a hereditary predisposition to VTE is suspected, the woman should be referred to a specialist for advice before deciding about any CHC use.

There is no consensus about the possible role of varicose veins and superficial thrombophlebitis in venous thromboembolism.

Symptoms of VTE (deep vein thrombosis and pulmonary embolism)

Women should be informed of the symptoms of VTE and be advised to seek urgent medical attention if VTE symptoms develop and to inform the healthcare professional that she is taking a CHC.

Symptoms of deep vein thrombosis (DVT) can include:

- unilateral swelling of the leg and/or foot or along a vein in the leg;
- pain or tenderness in the leg which may be felt only when standing or walking;
- increased warmth in the affected leg; red or discoloured skin on the leg.

Symptoms of pulmonary embolism (PE) can include:

- sudden onset of unexplained shortness of breath or rapid breathing;

- sudden coughing which may be associated with haemoptysis;
- sharp chest pain;
- severe light headedness or dizziness;
- rapid or irregular heartbeat.

Some of these symptoms (e.g. “shortness of breath”, “coughing”) are non-specific and might be misinterpreted as more common or less severe events (e.g. respiratory tract infections).

Other signs of vascular occlusion can include: sudden pain, swelling and slight blue discoloration of an extremity.

If the occlusion occurs in the eye symptoms can range from painless blurring of vision which can progress to loss of vision. Sometimes loss of vision can occur almost immediately.

Risk of arterial thromboembolism (ATE)

Epidemiological studies have associated the use of CHCs with an increased risk for arterial thromboembolism (e.g. myocardial infarction, angina pectoris, stroke or TIA). Arterial thromboembolic events may be fatal.

The risk of arterial thromboembolic complications in CHC users increases in women with risk factors. ZOELY is contraindicated if a woman has one serious or multiple risk factors for ATE that puts her at high risk of arterial thrombosis. If a woman has more than one risk factor, it is possible that the increase in risk is greater than the sum of the individual factors - in this case her total risk should be considered. If the balance of benefits and risks is considered to be negative a CHC should not be prescribed.

Risk factors for ATE

- Increasing age, particularly above 35 years
- Smoking
- Hypertension
- Obesity
- Positive family history (arterial thromboembolism ever in a sibling or parent especially at relatively early age e.g. below 50).
- Biochemical factors: hyperhomocysteinaemia and antiphospholipid antibodies (e.g. anticardiolipin antibodies~~,~~ and lupus anticoagulant), APC-resistance (including Factor V Leiden), antithrombin-III-deficiency, protein C deficiency, protein S deficiency.
- Migraine
- Other medical conditions associated with adverse vascular events:
    - Diabetes mellitus
    - Hyperhomocysteinaemia
    - Valvular heart disease
    - Atrial fibrillation
    - Dyslipoproteinaemia
    - Systemic lupus erythematosus

Women should be advised not to smoke if they wish to use a CHC. Women over 35years who continue to smoke should be strongly advised to use a different method of contraception.

If a hereditary predisposition is suspected, the woman should be referred to a specialist for advice before deciding about any CHC use.

An increase in frequency or severity of migraine during CHC use (which may be prodromal of a cerebrovascular event) may be a reason for immediate discontinuation.

Symptoms of ATE

Women should be informed of the symptoms of ATE and be advised to seek urgent medical attention if ATE symptoms develop and to inform the healthcare professional that she is taking a CHC.

Symptoms of a stroke can include:

- sudden numbness or weakness of the face, arm or leg, especially on one side of the body;
- sudden trouble walking, dizziness, loss of balance or coordination;
- sudden confusion, slurred speech or aphasia;
- sudden partial or complete loss of vision or diplopia;
- sudden, severe or prolonged headache with no known cause;
- loss of consciousness or fainting with or without seizure.

Temporary symptoms suggest the event is a transient ischaemic attack (TIA).

Symptoms of myocardial infarction (MI) can include:

- pain, discomfort, pressure, heaviness, sensation of squeezing or fullness in the chest, arm, or below the breastbone;
- discomfort radiating to the back, jaw, throat, arm, stomach;
- feeling of being full, having indigestion or choking;
- sweating, nausea, vomiting or dizziness;
- extreme weakness, anxiety, or shortness of breath;
- rapid or irregular heartbeats.

Neoplasms

- The most important risk factor for cervical cancer is persistent human papilloma virus (HPV) infection. Epidemiological studies have indicated that long-term use of ethinylestradiol-containing COCs contributes to this increased risk, but there continues to be uncertainty about the extent to which this finding is attributable to confounding effects, like increased cervical screening and difference in sexual behaviour including use of barrier contraceptives, or a causal association.
- With the use of the higher-dosed COCs (50 µg ethinylestradiol) the risk of endometrial and ovarian cancer is reduced. Whether this also applies to 17β-estradiol -containing COCs remains to be confirmed.
- A meta-analysis from 54 epidemiological studies reported that there is a slightly increased relative risk (RR = 1.24) of having breast cancer diagnosed in women who

are currently using ethinylestradiol-containing COCs. The excess risk gradually disappears during the course of the 10 years after cessation of COC use. Because breast cancer is rare in women under 40 years of age, the excess number of breast cancer diagnoses in current and recent COC users is small in relation to the overall risk of breast cancer. The breast cancers diagnosed in ever-users tend to be less advanced clinically than the cancers diagnosed in never-users.

- In another epidemiological study of 1.8 million Danish women followed an average of 10.9 years, the reported RR of breast cancer among COC users increased with longer duration of use compared with women who never used COCs (overall RR = 1.19; RR ranged from 1.17 for 1 to less than 5 years of use to 1.46 after more than 10 years of use). The reported absolute risk difference (number of breast cancer cases between never-users compared with current and recent COC users) was small: 13 per 100,000 woman-years.
- Epidemiological studies do not provide evidence for causation. The observed pattern of increased risk may be due to an earlier diagnosis of breast cancer in COC users, the biological effects of COCs or a combination of both.
- In rare cases, benign liver tumours, and even more rarely, malignant liver tumours have been reported in users of COCs. In isolated cases, these tumours have led to life-threatening intra-abdominal haemorrhages. Therefore, a hepatic tumour should be considered in the differential diagnosis when severe upper abdominal pain, liver enlargement or signs of intra-abdominal haemorrhage occur in women taking COCs.

Meningioma

The occurrence of meningiomas (single and multiple) has been reported in association with use of nomegestrol acetate, especially at high doses and for prolonged use (several years). Patients should be monitored for signs and symptoms of meningiomas in accordance with clinical practice. If a patient is diagnosed with meningioma, any nomegestrol acetate-containing treatment, must be stopped, as a precautionary measure.

Hepatitis C

During clinical trials with the Hepatitis C virus (HCV) combination drug regimen ombitasvir/paritaprevir/ritonavir and dasabuvir with and without ribavirin, ALT elevations greater than 5 times the upper limit of normal (ULN) were significantly more frequent in women using ethinylestradiol-containting medications such as CHCs. Additionally, also in patients treated with glecaprevir/pibrentasvir or sofosbuvir/velpatasvir/voxilaprevir, ALT elevations were observed in women using ethinylestradiol- containing medications such as CHCs.

Women using medications containing estrogens other than ethinylestradiol, such as estradiol and ombitasvir/paritaprevir/ritonavir and dasabuvir with or without ribavirin had a rate of ALT elevation similar to those not receiving any estrogens; however, due to the limited number of women taking these other estrogens, caution is warranted for co-administration with the following combination drug regimens: ombitasvir/paritaprevir/ritonavir and dasabuvir with or without ribavirin; glecaprevir/pibrentasvir or sofosbuvir/velpatasvir/ voxilaprevir (see Section 4.5 Interactions with other medicines and other forms of interactions).

Other conditions

- Women with hypertriglyceridaemia, or a family history thereof, may be at an increased risk of pancreatitis when using COCs.
- Although small increases in blood pressure have been reported in many women taking COCs, clinically relevant increases are rare. A relationship between COC use and clinical hypertension has not been established. However, if a sustained clinically significant hypertension develops during the use of a COC then it is prudent for the physician to suspend the intake of the tablets and treat the hypertension. Where considered appropriate, COC use may be resumed if normotensive values can be achieved with antihypertensive therapy. In seven multi-centre clinical trials of up to two years duration, no clinically relevant changes in blood pressure were observed with ZOELY.
- The following conditions have been reported to occur or deteriorate with both pregnancy and COC use, but the evidence of an association with COC use is inconclusive: jaundice and/or pruritus related to cholestasis; gallstone formation; porphyria; systemic lupus erythematosus; haemolytic uraemic syndrome; Sydenham's chorea; herpes gestationis; otosclerosis related hearing loss.
- Exogenous oestrogens may induce or exacerbate symptoms of hereditary and acquired angioedema.
- Acute or chronic disturbances of liver function may necessitate the discontinuation of COC use until markers of liver function return to normal. Recurrence of cholestatic jaundice which occurred first during pregnancy or previous use of sex steroids necessitates the discontinuation of COCs.
- There is no evidence for a need to alter the therapeutic regimen in diabetics using low-dose COCs (containing <0.05 mg ethinylestradiol). However, diabetic women should be carefully observed while taking a COC especially in the first months of use. ZOELY was shown to have no effect on peripheral insulin resistance and glucose tolerance in healthy women (see Section 5.1 Pharmacodynamic properties, Clinical trials).
- Crohn's disease, ulcerative colitis and worsening of depression have been associated with COC use.
- Chloasma may occasionally occur, especially in women with a history of chloasma gravidarum. Women with a tendency to chloasma should avoid exposure to the sun or ultraviolet radiation whilst taking COCs.
- ZOELY contains <60 mg lactose per tablet. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption who are on lactose-free diet should take this amount into consideration.
- Depressed mood and depression are well-known undesirable effects of hormonal contraceptive use (see Section 4.8 Adverse effects (Undesirable effects)). Depression can be serious and is a well-known risk factor for suicidal behaviour and suicide. Women should be advised to contact their physician in case of mood changes and depressive symptoms, including shortly after initiating the treatment.

Medical examination/consultation

Prior to the initiation or reinstitution of COC use, a complete medical history (including family history) should be taken and pregnancy must be ruled out. Blood pressure should be measured and if clinically indicated a physical examination should be performed, guided by the contraindications and precautions. The woman should also be instructed to carefully read the user leaflet and to adhere to the advice given. The frequency and nature of further periodic checks should be based on established practice guidelines and be adapted to the individual woman.

Women should be advised that oral contraceptives do not protect against HIV infections (AIDS) and other sexually transmitted diseases.

Reduced efficacy

The efficacy of COCs may be reduced in the event of e.g., missed tablets (see Section 4.2 Dose and method of administration), gastro-intestinal disturbances during active tablet taking (see Section 4.2 Dose and method of administration), or use of concomitant medication that decreases the plasma concentrations of nomegestrol acetate (see Section 4.5 Interactions with other medicines and other forms of interactions).

Cycle control

As with all COCs, breakthrough bleeding or spotting may occur, especially during the first months of use. Therefore, the evaluation of any breakthrough bleeding or spotting is only meaningful after an adaptation interval of about three cycles. If bleeding irregularities persist or occur after previously regular cycles, then non-hormonal causes should be considered and adequate diagnostic measures are indicated to exclude malignancy or pregnancy. These may include curettage. Women with undiagnosed abnormal vaginal bleeding should not start treatment with a COC until a possible underlying condition has been excluded.

In the pivotal efficacy and safety trials, women using ZOELY experienced overall a low number of bleeding events. Withdrawal bleedings were light and of short duration (on average 3-4 days) and often less painful (dysmenorrhea).

Some users of ZOELY have reported absence of withdrawal bleeding during the placebo yellow tablet phase although not being pregnant. In such cases, absence of withdrawal bleeding was not associated with a higher occurrence of breakthrough bleeding or spotting in the subsequent cycle.

If absence of withdrawal bleeding occurs and ZOELY is taken according to the instructions as described under Section 4.2 Dose and method of administration it is unlikely that the woman is pregnant. However, pregnancy must be ruled out before ZOELY use is continued if ZOELY has not been taken as directed or if two consecutive withdrawal bleeds are missed.

Use in hepatic impairment

See Section 4.3 Contraindications and Section 5.2 Pharmacokinetic properties, Special populations.

Use in renal impairment

See Section 5.2 Pharmacokinetic properties, Special populations.

Use in the elderly

No data available.

Paediatric use

Warnings and precautions for post-menarcheal adolescents less than 18 years of age and women greater than 50 years of age are expected to be similar to those described for adults between these age groups although this has not been confirmed in clinical trials.

Effect on laboratory tests

See Section 4.5 Interactions with other medicines and other forms of interactions, Effect on laboratory tests.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Note: The prescribing information of concomitant medications should be consulted to identify potential interactions.

Influence of other medicinal products on ZOELY
Interactions between oral contraceptives and other drugs may lead to breakthrough bleeding and/or contraceptive failure. The following interactions have been reported in the literature for COCs in general.

Hepatic metabolism: Interactions can occur with medicinal or herbal products that induce microsomal enzymes, specifically cytochrome P450 enzymes (CYP) which can result in increased clearance reducing plasma concentrations of sex hormones and may decrease the effectiveness of combined oral contraceptives, including ZOELY. These products include phenytoin, barbiturates, primidone, bosentan, carbamazepine, rifampicin, and possibly also oxcarbazepine, topiramate, felbamate, griseofulvin, products containing St. John’s wort and some HIV protease inhibitors (e.g. ritonavir and nelfinavir) and non-nucleoside reverse transcriptase inhibitors (e.g.nevirapine and efavirenz), and combinations of them.

Enzyme induction can occur after a few days of treatment. Maximal enzyme induction is generally observed within a few weeks. After drug therapy is discontinued, enzyme induction can last for about 28 days.

When co-administered with hormonal contraceptives, many combinations of HIV protease inhibitors (e.g. nelfinavir) and non-nucleoside reverse transcriptase inhibitors (e.g. nevirapine), and/or combinations with Hepatitis C virus (HCV) medicinal products (e.g., boceprevir, telaprevir), can increase or decrease plasma concentrations of progestins, including nomegestrol acetate, or estrogen. The net effect of these changes may be clinically relevant in some cases.

Women receiving any of the above-mentioned hepatic enzyme-inducing medicinal or herbal products should be advised that the efficacy of ZOELY may be reduced. A barrier contraceptive method should also be used during administration of the hepatic enzyme-inducing medicinal product, and for 28 days after discontinuation of the hepatic enzyme-inducing medicinal product.

If concomitant drug administration runs beyond the end of the active tablets in the current blister pack, the next blister pack should be started right away without the usual placebo tablet interval.

For women on long-term therapy with microsomal enzyme inducing medicinal products, an alternative method of contraception unaffected by enzyme-inducing medicinal products should be considered.

Concomitant administration of strong (e.g. ketoconazole, itraconazole, clarithromycin) or moderate (e.g. fluconazole, diltiazem, erythromycin) CYP3A inhibitors may increase the serum concentrations of estrogens or progestins.

Antibiotics: Contraceptive failures of ethinylestradiol-containing oral contraceptives have been reported with antibiotics, such as ampicillin and tetracyclines. The mechanism of this effect has not been elucidated and it is unknown whether interactions of antibiotics with a 17β-estradiol-containing contraceptive occur. Women on treatment with antibiotics (except rifampicin and griseofulvin, see above) should use a barrier method until 7 days after discontinuation. If the period during which the barrier method is used extends beyond the end of the white tablets in the COC pack, the yellow placebo tablets must be discarded and the next COC pack should be started right away.

Drug interaction studies were not performed with ZOELY, but two studies with rifampicin and ketoconazole, respectively, were performed with a higher dosed NOMAC-E2 combination (NOMAC 3.75 mg + 1.5 mg E2) in post-menopausal women.

Influence of ZOELY on other medicinal products
Oral contraceptives may affect the metabolism of other drugs. Accordingly, plasma and tissue concentrations may either increase (e.g. ciclosporin) or decrease (e.g. lamotrigine).

Direct acting antiviral agents (DAAs) and ethinylestradiol-containing medicinal products such as CHCs
During clinical trials with the HCV combination drug regimen ombitasvir/paritaprevir/ritonavir and dasabuvir with or without ribavirin, ALT elevations greater than 5 times the upper limit of normal (ULN) were significantly more frequent in women using ethinylestradiol-containing medications such as CHCs. Additionally, also in patients treated with glecaprevir/pibrentasvir or sofosbuvir/velpatasvir/voxilaprevir, ALT elevations were observed in women using ethinylestradiol-containing medications such as CHCs.

Direct acting antiviral agents (DAAs) and medicinal products containing estrogens other than ethinylestradiol, such as estradiol
Women using medications containing estrogens other than ethinylestradiol, such as estradiol and ombitasvir/paritaprevir/ritonavir and dasabuvir with or without ribavirin had a rate of ALT

elevation similar to those not receiving any estrogens; however, due to the limited number of women taking these other estrogens, caution is warranted for co-administration with the following combination drug regimens: ombitasvir/paritaprevir/ritonavir and dasabuvir with or without ribavirin; glecaprevir/pibrentasvir or sofosbuvir/velpatasvir/voxilaprevir (see Section 4.4 Special warnings and precautions for use).

Paediatric population
The interactions as described above are expected to be similar in postmenarcheal adolescent women.

Effect on laboratory tests

The use of contraceptive steroids may influence the results of certain laboratory tests, including biochemical parameters of liver, thyroid, adrenal and renal function, plasma levels of (carrier) proteins, e.g., corticosteroid binding globulin and lipid/lipoprotein fractions, parameters of carbohydrate metabolism and parameters of coagulation and fibrinolysis. Changes generally remain within the normal laboratory range.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

See Section 5.1 Pharmacodynamic properties.

Use in pregnancy

(Category B3)
ZOELY is not indicated during pregnancy. If pregnancy occurs during treatment with ZOELY, further intake should be stopped. Most epidemiological studies have revealed neither an increased risk of birth defects in children born to women who used ethinylestradiol-containing COCs prior to pregnancy, nor a teratogenic effect when ethinylestradiol-containing COCs were taken inadvertently during early pregnancy.

Clinical data on a limited number of exposed pregnancies indicate no adverse effect of ZOELY on the foetus or neonate.

In rats, treatment with nomegestrol acetate and estradiol in combination caused increased post-implantation loss, abortions, decreased foetal weight, feminisation of male foetuses, malformations (cleft palate and bent tail) and increased variations (vertebral and rib abnormalities and incomplete ossification). Nomegestrol acetate, given alone in rats, prolonged or impaired parturition. Post-implantation loss was increased and foetal weight was decreased in rabbits treated with the combination. Systemic exposure to nomegestrol acetate (plasma AUC) at no-effect doses in the animal embryofetal development studies was similar to or less than the expected human exposure level. Nomegestrol acetate was shown to cross the placenta in monkeys, with foetal plasma levels comparable to maternal drug levels.

Use in lactation

Lactation may be influenced by COCs as they may reduce the quantity and change the composition of breast milk. Therefore, the use of COCs should not be recommended until the

nursing mother has completely weaned her child. Small amounts of the contraceptive steroids and/or their metabolites may be excreted with the milk, but there is no evidence that this adversely affects infant health.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

ZOELY has no influence on the ability to drive and use machines.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

The most serious adverse reactions associated with the use of oral contraceptives are indicated under Section 4.4 Special warnings and precautions for use (see also Section 4.3 Contraindications).

Tabulated summary of adverse reactions
Seven multi-centre clinical trials of up to two years duration were used to evaluate the safety of ZOELY. In total 3,490 women, aged 18-50, were enrolled and completed 35,028 cycles.

ZOELY is well tolerated and demonstrates an overall safety profile similar to other combined oral contraceptives. Possibly related undesirable effects that have been reported in users of ZOELY are listed in the table below:

Table 2: Adverse reaction in MedDRA Term[1]

Body system	**Frequency**			
	Very common ≥ 1/10	**Common ≥ 1/100 to <1/10**	**Uncommon ≥ 1/1000 to < 1/100**	**Rare ≥1/10,000 to < 1/1000**
Metabolism and nutrition disorders			increased appetite, fluid retention	decreased appetite
Psychiatric disorders		decreased libido, depression/ depressed mood, mood altered		increased libido
Nervous system disorders		Headache, migraine		disturbance in attention
Eye disorders				dry eye, contact lens intolerance
Vascular disorders			hot flush	
Gastrointestinal disorders		nausea	abdominal distension	dry mouth
Skin and subcutaneous	acne[2]		hyperhydrosis, alopecia, pruritus,	chloasma, hypertrichosis

Body system	Frequency			
	Very common ≥ 1/10	**Common ≥ 1/100 to <1/10**	**Uncommon ≥ 1/1000 to < 1/100**	**Rare ≥1/10,000 to < 1/1000**
tissue disorders			dry skin, seborrhea	
Musculoskeletal and connective tissue disorders			sensation of heaviness	
Reproductive system and breast disorders	abnormal withdrawal bleeding	metrorrhagia, menorrhagia, breast pain, pelvic pain	hypomenorrhoea, breast swelling, galactorrhoea, uterine spasm, premenstrual syndrome, breast mass, dyspareunia, vulvovaginal dryness	vaginal odour, vulvovaginal discomfort
General disorders and administrative site conditions			irritability, oedema	hunger
Investigations		weight increased	hepatic enzyme increased	

[1] The most appropriate MedDRA term (version 13.1) to describe a certain adverse reaction is listed. Synonyms or related conditions are not listed, but should be taken into account as well.

[2] Acne was a solicited rather than spontaneously reported event, being assessed at every study visit.

The adverse reaction rates for ZOELY (N = 3490) in comparison to the reference COC containing drospirenone 3 mg – ethinylestradiol 30 µg (21/7 regimen) (N = 1105) in the integrated safety data set were: acne (15.4 % versus 7.9 %), weight increased (8.5 % versus 5.9 %) and abnormal withdrawal bleeding (predominantly absence of withdrawal bleeding) (10.2 % versus 0.6 %).

Description of selected adverse reactions

A number of undesirable effects have been reported in women using combined oral contraceptives containing ethinylestradiol, which are discussed in more detail in Section 4.4 Special warnings and precautions for use. These include:

- venous thromboembolic disorders;
- arterial thromboembolic disorders;
- hypertension;
- hormone-dependent tumours (e.g. liver tumours, breast cancer);
- chloasma.

The frequency of diagnosis of breast cancer is very slightly increased among COC users. As breast cancer is rare in women under 40 years of age the excess number is small in relation to the overall risk of breast cancer. Causation with COC use is unknown. For further information, see Section 4.3 Contraindications and Section 4.4 Special warnings and precautions for use.

Paediatric population
Frequency, type and severity of adverse reactions in post-menarcheal adolescents are expected to be the same as in adult women.

Other special populations
No studies have been performed with renally or hepatically impaired subjects. However, steroid hormones may be poorly metabolized in patients with impaired liver function.

Post-market experience
In addition to the above mentioned adverse reactions, hypersensitivity reactions have been reported in ZOELY users (frequency unknown).

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at http://www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

There have been no reports of serious deleterious effects from overdose. Multiple doses up to five times the daily dose of ZOELY and single doses up to 40 times the daily dose of nomegestrol acetate alone have been used in women without safety concern. On the basis of general experience with combined oral contraceptives, symptoms that may occur are: nausea, vomiting and, in young girls, slight vaginal bleeding. There are no antidotes and further treatment should be symptomatic.

For information on the management of overdose, contact the Poisons Information Centre on 131126 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action

Nomegestrol acetate is a highly selective progestogen derived from, and structurally similar to, the naturally occurring steroid hormone, progesterone. Nomegestrol acetate has a strong affinity for the human progesterone receptor and has strong anti-gonadotropic activity, moderate anti-androgenic activity, and is devoid of any estrogenic, androgenic, glucocorticoid or mineralocorticoid activity.

The estrogen contained in ZOELY is 17β-estradiol, a natural estrogen identical to the endogenous human 17β-estradiol (E2). This estrogen differs from the estrogen ethinylestradiol used in other combined oral contraceptives (COC) by the lack of the ethinyl group in the 17alpha position. During use of ZOELY, the average E2 levels are comparable to the E2 levels during the early follicular and late luteal phase of the menstrual cycle.

The contraceptive effect of ZOELY is based on the interaction of various factors, the most important of which are the inhibition of ovulation and the changes in the cervical secretion. During the use of ZOELY, nomegestrol acetate is primarily responsible for the suppression of ovulation, with 17β-estradiol enhancing the suppressive effects of nomegestrol acetate.

After discontinuation of ZOELY, rapid return to ovulation was observed in most women.

Folic acid is an important vitamin in the early phase of pregnancy. Folic acid serum levels remained unchanged during and after ZOELY treatment for 6 consecutive cycles as compared to baseline.

Pharmacotherapeutic group: progestagens and estrogens, fixed combinations, ATC code: G03A A14.

Clinical trials

Contraceptive efficacy

Two randomized, open-label, comparative efficacy-safety trials (Study report 292001 and 292002) were conducted in more than 3200 women treated for 13 consecutive cycles with ZOELY. The primary efficacy and safety parameters were contraceptive efficacy, vaginal bleeding pattern (cycle control), general safety and acceptability. Women entering the study were aged between 18 and 50 years and women with a BMI greater than 35 were excluded from the study. Women were excluded from the study if they had conditions which were listed as a contraindication for combined oral contraceptives. The overall Pearl Index (method failure and user failure) 18-50 years of age was: 0.64 (upper limit 95% CI 1.03).

In the pivotal efficacy and safety trials, women using ZOELY experienced overall a low number of bleeding events. Withdrawal bleedings were light and of short duration (on average 3-4 days) and often less painful (dysmenorrhea).

A randomized, open-label, comparative, multicenter trial (Study report 292004) was performed to assess effects of ZOELY on haemostasis, lipids, carbohydrate metabolism, adrenal and thyroid function and on androgens. Glucose tolerance and insulin sensitivity remained unaltered and no clinically relevant effects on lipid metabolism and haemostasis were observed with ZOELY. The comparator levonorgestrel 150µg + ethinylestradiol 30µg was associated with more pronounced changes in these parameters. ZOELY increased the carrier proteins TBG and CBG, but to lesser extent than LNG-EE. ZOELY induced a small increase in SHBG, which was slightly higher than LNG-EE (20 to 30 µg EE). The androgenic parameters androstenedione, DHEA-S, total and free testosterone were significantly reduced during use of ZOELY.

Endometrial histology was investigated in a subgroup of women (n=32) in one clinical study after 13 cycles of treatment. There were no abnormal results.

5.2 PHARMACOKINETIC PROPERTIES

Nomegestrol acetate (NOMAC)

Absorption

Orally administered nomegestrol acetate (NOMAC) is rapidly absorbed. Maximum plasma concentrations of NOMAC of about 7 ng/mL are reached at 2 h after single administration. The absolute bioavailability of NOMAC after a single dose is 63 %. Administration of ZOELY with a high fat meal increased the bioavailability of NOMAC by 27-29% which was not considered clinically relevant.

Distribution

Nomegestrol acetate (NOMAC) is extensively bound to albumin (97-98%), but does not bind to sex hormone binding globulin (SHBG) or corticoid binding globulin (CBG). The apparent volume of distribution of NOMAC at steady state is 1645 ± 576L.

Metabolism

Nomegestrol acetate (NOMAC) is metabolized into several hydroxylated metabolites without progestagenic activity, by liver cytochrome P450 enzymes, mainly CYP2C8, CYP2C19, CYP3A4 and CYP3A5. NOMAC and its hydroxylated metabolites undergo extensive phase 2 metabolism to form glucuronide and sulphate conjugates. The estrogenic and androgenic activities of the metabolites are unknown. The apparent clearance at steady state is 26 L/h.

Excretion

The elimination half life ($t_{1/2}$) is 46 hours (ranging from 28-83 hours) at steady state. The elimination half-life of metabolites was not determined. NOMAC is excreted via urine and faeces. Approximately 80% of the dose is excreted in urine and faeces within 4 days. Excretion of NOMAC was nearly complete after 10 days and amounts excreted were higher in faeces than in urine.

Linearity
Dose-linearity was observed in the range 0.625 – 5 mg (assessed in fertile and post-menopausal women).

Steady-State Conditions
The pharmacokinetics of nomegestrol acetate (NOMAC) are not influenced by SHBG. Steady-state is achieved after 5 days. Maximum plasma concentrations of NOMAC of about 12 ng/mL are reached 1.5 hours after dosing. Average steady state plasma concentrations are 4 ng/mL.

Drug-drug interactions
From *in vitro* studies, nomegestrol acetate causes no notable induction or inhibition of any cytochrome P450 enzymes and has no clinically relevant interaction with the P-gp transporter.

Estradiol (E2)

Absorption

17β-Estradiol (E2) is subject to a substantial first-pass effect after oral administration. The absolute bioavailability is approximately 5%. After administration of ZOELY with a high fat meal, the mean exposure to estradiol (E2) was only marginally affected. Exposure to the major metabolite of E2, estrone (E1), was increased by about 20% which was not considered clinically relevant.

Distribution

The distribution of exogenous and endogenous 17β-estradiol (E2) is similar. Estrogens are widely distributed in the body and are generally found in higher concentrations in the sex hormone target organs. Estradiol circulates in the blood bound to SHBG (37%) and to albumin (61%), while only approximately 1-2% is unbound.

Metabolism

Oral exogenous 17β-estradiol (E2) is extensively metabolized. The metabolism of exogenous and endogenous E2 is similar. E2 is rapidly transformed in the gut and the liver in several metabolites, mainly estrone (E1), which are subsequently conjugated and undergo entero-hepatic circulation. There is a dynamic equilibrium between E2, E1 and E1-Sulfate (E1S) due to various enzymatic activities including E2-dehydrogenases, sulfotransferases and aryl sulfatases. Oxidation of E1 and E2 involves cytochrome P450 enzymes, mainly CYP1A2, CYP1A2 (extra hepatic), CYP3A4, CYP3A5, and CYP1B1 and CYP2C9.

Excretion

17β-Estradiol (E2) is rapidly cleared from the circulation. Due to metabolism and enterohepatic circulation, a large circulating pool of estrogen sulfates and glucuronides is present. This results in a highly variable elimination half-life of E2, which is calculated to be 8.4 ± 6.4 hours, after intravenous administration.

Steady-State Conditions
Maximum serum concentrations of 17β-estradiol (E2) are about 90 pg/mL and are reached 6 hours after dosing. Average serum concentrations are 50 pg/mL and these E2 levels correspond with the early and late phase of a woman's menstrual cycle.

Special populations

Paediatric population
Whole-body-physiologically based pharmacokinetic modeling and simulation showed that no difference in the nomegestrol acetate pharmacokinetics is expected between post-menarcheal adolescent women (aged 12-17 years) and adult women.

Effect of renal impairment
No studies were performed to evaluate the effect of renal disease on the pharmacokinetics of ZOELY.

Effect of hepatic impairment
No studies were conducted to evaluate the effect of hepatic disease on the pharmacokinetics of ZOELY. However, steroid hormones may be poorly metabolised in women with impaired liver function.

Ethnic groups
No formal studies were performed to assess pharmacokinetics in ethnic groups.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

No evidence for genotoxicity was found with nomegestrol acetate in assays for bacterial and mammalian mutagenicity, yeast mitotic gene conversion, chromosomal aberrations and unscheduled DNA synthesis *in vitro* and clastogenicity *in vivo* (mouse and rat bone marrow micronucleus tests).

There is limited evidence available in the literature suggesting that estradiol may be weakly genotoxic at high doses. No evidence could be found for an increase in the rate of gene mutation in bacterial or mammalian cells, but there was some evidence for the induction of chromosomal aberrations and aneuploidy and an increased incidence of sister chromatid exchanges (indicative of DNA damage) in mammalian cells. None of these effects were induced by estradiol in human lymphocyte cultures. Importantly, there was no evidence for micronuclei formation in rodent bone marrow assays.

The genotoxic potential of the combination of nomegestrol acetate and estradiol has not been investigated.

Carcinogenicity

Carcinogenicity studies have not been performed with the combination of nomegestrol acetate and estradiol. However, studies have been performed for the two active components separately.

Supraphysiological doses of estradiol have been associated with the induction of tumours in estrogen-dependent target organs in all rodent species tested. The relevance of these findings with respect to humans has not been established. However, it must be borne in mind that sex steroids can promote the growth of certain hormone-dependent tissues and tumours.

In a long-term oral (dietary) carcinogenicity study in mice, nomegestrol acetate increased the incidence of mammary gland carcinoma and pituitary adenoma in females at doses ≥20 mg/kg/day and 50 mg/kg/day, respectively. Systemic exposure to nomegestrol acetate (plasma AUC) in animals at these doses was 4 to 15 times higher than that of women treated with ZOELY. These findings are consistent with extensive endocrine disruption in the species caused by the progestagenic activity of nomegestrol acetate.

No evidence of tumourigenicity was found with nomegestrol acetate in a 2-year study in rats using dietary doses up to 10 mg/kg/day (yielding 30 times the expected human exposure level).

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

The white active tablets contain the inactive ingredients lactose monohydrate, microcrystalline cellulose, crospovidone, purified talc, magnesium stearate, colloidal anhydrous silica, OPADRY II complete film coating system 85F18422 White PI (11376).

The yellow placebo tablets contain the inactive ingredients lactose monohydrate, microcrystalline cellulose, crospovidone, purified talc, magnesium stearate, colloidal anhydrous silica, OPADRY II complete film coating system 85F32865 Yellow PI (106699).

6.2 INCOMPATIBILITIES

Not applicable.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 30˚C.

6.5 NATURE AND CONTENTS OF CONTAINER

Pack sizes: 1 x 28 and 3 x 28 tablets in PVC/Al blisters (transparent PVC thermoforming film with aluminium lidding foil). Not all pack sizes may be marketed.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

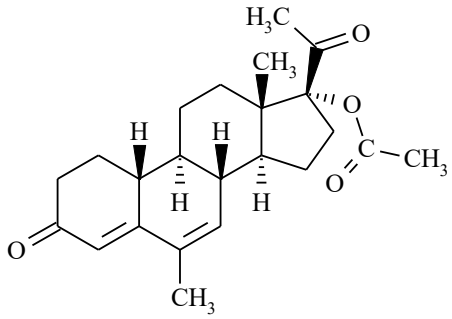
In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

ZOELY is a combined oral contraceptive (COC) preparation containing the progestogen nomegestrol acetate and the natural estrogen 17β-estradiol as the active substances.

Chemical structure

Nomegestrol acetate



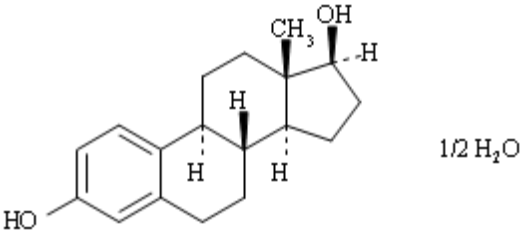
Chemical name: 17α-acetoxy-6-methyl-19-norpregna-4,6-dien-3,20-dione

Molecular formula: $C_{23}H_{30}O_4$

Molecular mass: 370.48

A white to off white crystalline powder that is freely soluble in methylene chloride, acetone and ethyl acetate, soluble in dioxane and acetonitrile and sparing soluble in methanol and ethanol. Melting range is between 177 and 180°C.

Estradiol



Chemical name: estra-1,3,5(10)-triene-3,17β-diol

Molecular formula: $C_{18}H_{24}O_2$

Molecular mass: 281.4

A white to almost white, crystalline powder and is practically insoluble in water. Melting range is between 173 and 179°C.

CAS number

Nomegestrol acetate: 58652-20-3
Estradiol: 50-28-2

7 MEDICINE SCHEDULE (POISONS STANDARD)

Schedule 4

8 SPONSOR

Theramex Australia Pty Ltd
Level 22, 60 Margaret Street,
Sydney NSW 2000
1800 THERAMEX or 1800 843 726

9 DATE OF FIRST APPROVAL

15 August 2011

10 DATE OF REVISION

25 August 2025

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
4.4	Expanded warning related to use with hepatitis C virus treatment regimes, expanded warning in relation to exogenous estrogens, added warning related to depression.
4.5	Expanded information relating to hepatitis C virus treatment regimes
All	Minor editorial changes to improve readability.